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(54) Title: PROCESS FOR SOLUBILIZING DIFFICULTLY SOLUBLE PHARMACEUTICAL ACTIVES			
(57) Abstract <p>The present invention relates to a process for solubilizing at least one difficultly soluble pharmaceutical active in a mixture of polyethylene glycol and polyvinylpyrrolidone. The process does not require water as a solvent or the use of a heating step. In further embodiments, the present invention also relates to a process for encapsulating these solubilized pharmaceutical compositions within soft gelatin shells, which are preferably transparent. Both the resulting compositions and their capsules provide an effective means for oral delivery of a wide variety of difficultly soluble pharmaceutical actives.</p>			

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PROCESS FOR SOLUBILIZING DIFFICULTLY SOLUBLE PHARMACEUTICAL ACTIVESTECHNICAL FIELD

5 The present invention relates to a process for solubilizing at least one difficultly soluble pharmaceutical active in a mixture of polyethylene glycol and polyvinylpyrrolidone. In further embodiments, the present invention also relates to a process for encapsulating these solubilized pharmaceutical compositions within soft gelatin shells, which are optionally transparent. Both the 10 resulting compositions and their capsules provide an effective means for oral delivery of a wide variety of difficultly soluble pharmaceutical actives.

BACKGROUND OF THE INVENTION

15 Liquid, and especially concentrated liquid pharmaceutical compositions offer many advantages over solid compositions. Liquids are easy to swallow and provide an excellent vehicle for the uniform delivery of pharmaceutical actives. Liquids provide a rapid onset of pharmacologic action, since the composition does not first have to disintegrate and dissolve in the gastrointestinal tract. 20 Concentrated liquid compositions are ideally suited for encapsulation within a soft gelatin shell, to provide a portable and easy-to-swallow soft, flexible capsule. Encapsulation would also permit the accurate and uniform delivery of a unit dose of a pharmaceutical active, an advantage which becomes especially 25 important when relatively small amounts of an active are to be delivered. Additionally, soft gelatin capsules are aesthetically appealing (especially when filled with a transparent liquid) and can be manufactured in a wide variety of sizes, shapes, and colors.

30 However, despite these advantages of liquid compositions, it is not always possible to prepare a liquid composition of the desired pharmaceutical active. Many pharmaceutical actives are poorly soluble and therefore require relatively large volumes of solvent for dissolution. Also, the choice of solvents available for use in liquid compositions is limited by safety, compatibility, stability, 35 and economic concerns. Furthermore, the use of large volumes of

solvents for solubilizing pharmaceutical actives is undesirable because the resulting solutions would be so dilute as to require impractically large dosages for delivering a therapeutically effective amount of active. It would thus be difficult, if not impossible, to encapsulate such large volumes into only one or two gelatin capsules and yet have them be of a reasonable size for easy swallowing.

One approach to overcoming these solubility problems has been to incorporate water, water-miscible co-solvents, and surfactants into the compositions. See U.S. Patent No. 4,794,117, to Corbiere, issued December 27, 1988 which discloses the solubilization of hydrophobic pharmaceuticals in aqueous solutions of polyethylene glycol at controlled pH; U.S. Patent No. 4,690,823, to Lohner et al., issued September 1, 1987 which discloses the solubilization of ibuprofen in a mixture of polyethylene glycol and a surfactant; U.S. Patent No. 3,784,684, to Bossert et al., issued January 8, 1974 which discloses the solubilization of a pharmaceutical active in a mixture of polyethylene glycol and an alcohol having 2-8 carbons and 1-3 hydroxy groups; PCT Application No. WO88/02625, to Yu et al., published April 21, 1988 which discloses the solubilization of an ionized or partly-ionized pharmaceutical active in a mixture of water, polyethylene glycol, and polyvinylpyrrolidone; and European Patent Application No. 152,292, to Rogers, published August 21, 1985 which discloses acetaminophen formulations containing polyethylene glycol, an acrylic acid resin, and a surfactant.

In many instances it may not be possible or desirable to incorporate water, water-miscible co-solvents, or surfactants into a pharmaceutical composition. For example, water-miscible co-solvents, such as ethanol, have the disadvantage of being relatively volatile, thereby resulting in concentration changes in the actives over time. Also, these co-solvents may not be compatible with the desired pharmaceutical actives. A more important disadvantage of water and volatile water-miscible co-solvents is that they are incompatible with soft gelatin capsules. Even though it may be possible to prepare soft gelatin capsules containing these solvents, over time the capsules gradually soften and deform, and develop leaks as these solvents dissolve the

5 soft gelatin shell. Thus, it would be highly desirable to develop a solubilization process which does not require the use of water; and in processes where water-miscible co-solvents are used, it would be highly desirable to develop a process in which the water-miscible solvents are ultimately removed from the final compositions.

10 Previous investigators have attempted to circumvent these incompatibility problems by modifying the composition of the capsule shell. For example, U.S. Patent No. 3,865,603, to Szymanski et al., issued February 11, 1975 discloses gelatin compositions which are extended with chemically modified fluidity starches; U.S. Patent No. 2,580,683, to Kreuger, issued January 1, 1952 discloses gelatin compositions modified by the addition of non-hygroscopic water soluble substances; and Japanese Patent No. 84044096, to Morishita, issued January 26, 1984 discloses gelatin shells modified with tannic acid, and sugar and/or sugar derivatives. However, it may not always be desirable, feasible or economical to modify the soft gelatin shell with such additives. Thus, it would be highly desirable to find a solubilizing system for pharmaceutical actives which would also be compatible with soft gelatin shells.

20 15 20 Many processes for solubilizing pharmaceutical actives employ heat. However, heating the mixture is not always feasible or desirable because of stability concerns and the additional equipment, time, and costs associated with utilizing a heating process. Thus, it would be highly desirable to develop a solubilization process not requiring the use of heat.

25 30 35 The solubilization process of the present invention overcomes the disadvantages of the prior art by not requiring the use of water as a solvent, except for the minor amounts of water normally present in the materials employed and/or which is absorbed from the environment. Thus, the concentrated pharmaceutical compositions of the instant invention are substantially free of water. Importantly, the process of the present invention does not require a heating step.

It is therefore an object of the present invention to provide a process for solubilizing difficultly soluble pharmaceutical actives. Another object of the present invention is to provide a solubilization process which does not require water as a solvent or

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the use of a heating step. A further object of the present invention is to provide a process for preparing soft gelatin capsules containing a solution of a difficultly soluble pharmaceutical active, in which the soft gelatin shell is optionally transparent. A still further object of the present invention is to provide pharmaceutical compositions containing difficultly soluble pharmaceutical actives. An even further object of the present invention is to provide soft gelatin capsules containing a solution of a difficultly soluble pharmaceutical active, in which the soft gelatin shell is optionally transparent.

These and other objects of this invention will become apparent in light of the following disclosure.

#### SUMMARY OF THE INVENTION

The present invention relates to a process for solubilizing difficultly soluble pharmaceutical actives, comprising the steps of:

- (a) combining and mixing until dissolved
  - (i) from about 1% to about 40% of at least one difficultly soluble pharmaceutical active,
  - (ii) from about 20% to about 70% of a polyethylene glycol,
  - (iii) from about 1% to about 28% of a polyvinyl-pyrrolidone, and
  - (iv) from about 1% to about 50% of a solvent selected from the group consisting of monohydric alcohols having from 1 to 4 carbon atoms and mixtures thereof,
- 20 wherein the ratio of said polyethylene glycol to said polyvinylpyrrolidone is at least about 2.5:1; and
- (b) evaporating said solvent to obtain a composition containing from about 0.1% to about 6% by weight of said solvent.

The present invention also relates to a process for preparing soft gelatin capsules containing a solution of a difficultly soluble pharmaceutical active, and to the compositions and the filled capsules themselves.

All percentages and ratios used herein are by weight and all measurements are at 25°C, unless otherwise indicated.

DETAILED DESCRIPTION OF THE INVENTION

The term "difficultly soluble pharmaceutical active", as used herein, describes an active having a solubility of less than or equal to 1% by weight in water at 25°C. This term is defined to also include the descriptive terms "sparingly soluble"; "slightly soluble"; "very slightly soluble"; "practically insoluble, or insoluble"; and their equivalents as defined in the USP XXII, p.8 (1990), this reference being incorporated herein by reference in its entirety.

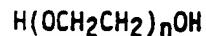
The term "substantially free of water", as used herein, describes highly concentrated pharmaceutical compositions which, as initially prepared, do not contain any water, except for the minor amounts of water normally present in the materials employed in their preparation and/or which is gradually absorbed from the environment or the optional gelatin shell; i.e., less than from about 0.1% to about 8% water, preferably less than from about 0.1% to about 6% water, more preferably less than from about 0.1% to about 4% water, and most preferably less than from about 0.1% to about 2% water. The term "as initially prepared", as used herein, is defined to mean the period of time from when the evaporation step is completed to about 5 minutes thereafter.

Concentrated Liquid Pharmaceutical Compositions

The highly concentrated liquid pharmaceutical compositions of the present invention comprise the following essential, as well as optional, components.

Polyethylene Glycol

An essential component of the present compositions is a polyethylene glycol. Polyethylene glycols generally are clear, viscous liquids or white solids which are soluble in water and many organic solvents. These polymers correspond to the general formula:



where  $n$  is greater than or equal to 4. Polyethylene glycols are described in G.M. Powell, III in Handbook of Water-Soluble Gums & Resins, R.L. Davidson, Ed. (McGraw-Hill, New York, 1980) pp. 18/1-18/31, this reference being incorporated herein by reference in its entirety. Polyethylene glycols, which are also known as "PEGs" or "polyoxyethylenes", are designated by both their average

5 molecular weight range and their average "n" value as in the above designated formula. For example, polyethylene glycol 400, which is also known by the CTFA designation, PEG-8, has an average molecular weight range from 380-420 and an average value of n between 8.2 and 9.1. See CTFA Cosmetic Ingredient Dictionary, Third Edition (1982), pp. 201-203; and The Merck Index, Tenth Edition, entry 7441, p. 1092 (1983); these two references being incorporated herein by reference in their entirety.

10 The polyethylene glycols useful herein are those which are liquids at room temperature or have a melting point slightly thereabove. Preferred are the polyethylene glycols having a molecular weight range from about 300 to about 1000 and corresponding n values from about 6 to about 20. More preferred are the polyethylene glycols having a molecular weight range from about 15 400 to about 1000 and corresponding n values from about 8 to about 20. Most preferred are the polyethylene glycols having a molecular weight range from about 600 to about 1000 and corresponding n values from about 12 to about 20. Most especially preferred is a 20 polyethylene glycol having a molecular weight of about 600 and a corresponding n value of about 12. Moreover, mixtures of two or more polyethylene glycols of different average molecular weight range or n value can also be employed in the present invention. Liquid and low-melting polyethylene glycols are commercially 25 available from Union Carbide (Danbury, CT) under the Carbowax<sup>R</sup> trademark. See "Carbowax<sup>R</sup> Polyethylene Glycols", Union Carbide Technical Bulletin f-4772M-ICD 11/86-20M, this reference being incorporated herein by reference in its entirety.

30 Polyethylene glycols having an average molecular weight below about 300 are not desirable for use in the instant invention since such polyethylene glycols tend to diffuse into, plasticize, and ultimately disrupt the soft gelatin shells which can be employed to 35 encapsulate the compositions described herein.

The process for preparing the highly concentrated liquid compositions of the present invention comprises adding from about 20% to about 70% polyethylene glycol, more preferably from about 30% to about 60%, and most preferably from about 40% to about 50%.

After the evaporation step, the resulting highly concentrated liquid compositions of the present invention comprise from about 25% to about 87.5% polyethylene glycol, more preferably from about 37.5% to about 75%, and most preferably from about 50% to about 75%.

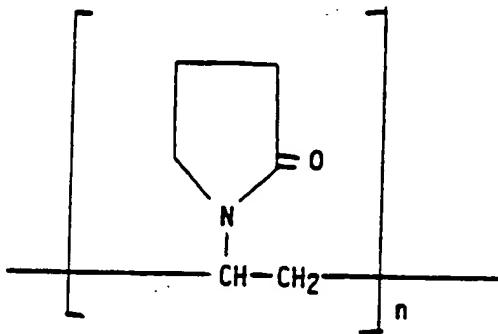
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Polyvinylpyrrolidone

An essential component of the present compositions is polyvinylpyrrolidone ("PVP"), which is a polymer of N-vinyl-2-pyrrolidone having the following formula:

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Polyvinylpyrrolidones are described in L. Blecher et al. in Handbook of Water-Soluble Gums & Resins, R.L. Davidson, Ed. (McGraw-Hill, New York, 1980) pp. 21/1-21/21, this reference being incorporated herein by reference in its entirety. Polyvinylpyrrolidone has different solubility characteristics based on its polymeric structure. Long-chain polyvinylpyrrolidone, which is also known as povidone, has good solubility in water and a number of organic solvents. Cross-linked polyvinylpyrrolidone, which is also known as crospovidone, is insoluble in virtually all common solvents. Both the soluble and insoluble forms of polyvinylpyrrolidone are commercially available from GAF Chemicals Company (Wayne, NJ) under the Plasdone<sup>R</sup> and Polyplasdone<sup>R</sup> trademarks, respectively, and from BASF Aktiengesellschaft (Ludwigshafen, Germany) under the Kollidon<sup>R</sup> trademark. Soluble forms of polyvinylpyrrolidone include Plasdone<sup>R</sup> K-25, Plasdone<sup>R</sup> K-26/28, Plasdone<sup>R</sup> K-29/32, Plasdone<sup>R</sup> C-15, Plasdone<sup>R</sup> C-30, Plasdone<sup>R</sup> C-90, Kollidon<sup>R</sup> 12 PF, Kollidon<sup>R</sup> 17 PF, Kollidon<sup>R</sup> 25, Kollidon<sup>R</sup> 30, and Kollidon<sup>R</sup> 90. Insoluble forms of polyvinylpyrrolidone include Polyplasdone XL<sup>R</sup>, Polyplasdone XL<sup>R</sup>10, Kollidon<sup>R</sup> CL, and Kollidon<sup>R</sup> CL-M. See "Tableting With Plasdone<sup>R</sup>", GAF Technical Bulletin 2302-110R1 (1986); "Polyplasdone XL<sup>R</sup>, Polyplasdone XL<sup>R</sup>10", GAF Technical Bulletin 2302-099 R2 (1984); and

"Kollidon<sup>R</sup> Grades, Polyvinylpyrrolidone for the Pharmaceutical Industry", BASF Technical Bulletin MEF 129e, Register 2, May 1986 (Bn); these references being incorporated herein by reference in their entirety.

5 The soluble forms of polyvinylpyrrolidone are preferred for use in the present invention. Preferred are soluble polyvinylpyrrolidones having an average molecular weight in the range from about 2900 to about 1,100,000; more preferred are those having an average molecular weight in the range from about 9000 to about 10  
10 45,000; and most preferred are those having an average molecular weight of about 29,000. Moreover, mixtures of two or more soluble polyvinylpyrrolidones of different average molecular weight can be employed.

15 The process for preparing the highly concentrated liquid compositions of the instant invention comprises adding from about 1% to about 28% of a soluble polyvinylpyrrolidone, more preferably from about 1% to about 10%, and most preferably from about 1% to about 5%.

20 After the evaporation step, the resulting highly concentrated liquid compositions of the instant invention comprise from about 1.25% to about 35% of a soluble polyvinylpyrrolidone, more preferably from about 1.25% to about 12.5%, and most preferably from about 1.25% to about 6.25%.

25 An important requirement of the processes and compositions of the instant invention is that the polyethylene glycol component(s) and the polyvinylpyrrolidone component(s) are present in a proper ratio. Preferably, the ratio of the total amount of polyethylene glycol to polyvinylpyrrolidone should be at least about 2.5:1.

#### Difficultly Soluble Pharmaceutical Actives

30 The compositions of the instant invention contain at least one difficultly soluble pharmaceutical active as an essential component. In general, these actives have a solubility less than or equal to about 1 percent by weight in water at 25°C. Useful classes of pharmaceutically-active compounds which can be incorporated into the 35 present compositions include analgesics, anti-inflammatory agents, anti-pyretics, calcium channel blockers, beta-blockers, antibacterials, antidepressants, antidiabetics, anti-emetics,

5 antihistamines, cerebral stimulants, sedatives, anti-parasitics, expectorants, diuretics, decongestants, antitussives, muscle relaxants, anti-Parkinsonian agents, bronchodilators, cardiotonics, antibiotics, antivirals, nutritional supplements (such as vitamins, minerals, fatty acids, amino acids, and the like), and mixtures thereof. Difficultly soluble pharmaceutical actives selected from the non-narcotic analgesics/nonsteroidal anti-inflammatory drugs are especially useful in the present invention. Examples of such drugs are disclosed in U.S. Patent No. 4,522,828, to Sunshine et al., 10 issued June 11, 1985; this patent being incorporated herein by reference in its entirety.

15 Examples of preferred difficultly soluble pharmaceutical actives useful in the present invention include, but are not limited to, acetaminophen, acetylsalicylic acid, ibuprofen, fenuprofen, fenoprofen, flurbiprofen, indomethacin, ketoprofen, naproxen, their pharmaceutically-acceptable salts, and mixtures thereof. Acetaminophen is especially preferred for use in the compositions of the present invention.

20 The process for preparing the highly concentrated liquid compositions of the instant invention comprises adding from about 1% to about 40% of a difficultly soluble pharmaceutical active, more preferably from about 15% to about 35%, and most preferably from about 20% to about 30%.

25 After the evaporation step, the resulting highly concentrated liquid compositions of the instant invention comprise from about 1.25% to about 50% of a difficultly soluble pharmaceutical active, more preferably from about 18.75% to about 43.75%, and most preferably from about 25% to about 37.5%.

#### Solvents

30 A solvent selected from the group consisting of the monohydric alcohols having from one to four carbon atoms, and mixtures thereof, is an essential component of the processes of the instant invention.

35 A sufficient quantity of solvent is utilized to aid in the solubilization of the essential components. By "sufficient" is meant a quantity of solvent that will ensure solubility of the components of the composition and yet not dilute the composition to the point where it occupies an unreasonably large volume. After

mixing and solubilization of the the components of the instant invention, the solvent is removed using standard evaporation techniques until the composition is substantially free from solvent. The term "substantially free from solvent" is herein defined to mean that the compositions of the present invention comprise within after about 5 minutes of the evaporation step no more than from about 0.1% to about 6% of solvent after the evaporation step. Ethanol is most preferred as the solvent for use in the processes of the instant invention.

10 The process for preparing the highly concentrated liquid compositions of the instant invention comprises adding from about 1% to about 50% of solvent, more preferably from about 5% to about 40%, and most preferably from about 10% to about 30%.

15 After the evaporation step, the resulting highly concentrated liquid compositions of the instant invention comprise no more than from about 0.1% to about 6% solvent.

Additional Pharmaceutical Actives

20 The compositions of the instant invention can also contain one or more additional pharmaceutical actives having a solubility greater than the difficultly soluble pharmaceutical actives described above. In general, these actives have a solubility greater than about 1 percent by weight in water at 25°C. Useful classes of additional pharmaceutically-active compounds include analgesics, anti-inflammatory agents, antipyretics, calcium channel blockers, beta-blockers, antibacterials, antidepressants, 25 antidiabetics, anti-emetics, antihistamines, cerebral stimulants, sedatives, anti-parasitics, expectorants, diruetics, decongestants, antitussives, muscle relaxants, anti-Parkinsonian agents, bronchodilators, cardiotonics, antibiotics, antivirals, nutritional supplements (such as vitamins, minerals, fatty acids, amino acids, 30 and the like), and mixtures thereof.

35 Examples of additional pharmaceutical actives useful in the present invention include, but are not limited to, pseudoephedrine and its salts such as pseudoephedrine hydrochloride; dextromethorphan and its salts such as dextromethorphan hydrobromide; doxylamine and its salts such as doxylamine succinate; phenindamine and its salts such as phenindamine hydrogen tartrate;

pheniramine and its salts such as pheniramine maleate; chlorpheniramine and its salts such as chlorpheniramine maleate; ephedrine and its salts such as ephedrine sulfate; triprolidine and its salts such as triprolidine hydrochloride; diphenhydramine and its salts such as diphenhydramine hydrochloride, diphenhydramine citrate, and diphenhydramine 8-chlorotheophyllinate; phenyltolamine and its salts; guaifenesin; phenylpropanolamine hydrochloride; and mixtures thereof. Preferred additional pharmaceutical actives are dextromethorphan hydrobromide, doxylamine succinate, pseudoephedrine hydrochloride, chlorpheniramine maleate, guaifenesin, triprolidine hydrochloride, diphenhydramine hydrochloride and mixtures thereof.

The process for preparing the highly concentrated liquid compositions of the instant invention optionally comprises adding from about 0.5% to about 20% of a second pharmaceutical active, or mixtures thereof.

After the evaporation step, the resulting highly concentrated liquid compositions of the instant invention can optionally comprise from about 0.625% to about 25% of a second pharmaceutical active, or mixtures thereof.

Optional Components

Other components which can be incorporated into the compositions of the instant invention include colorings, flavorings, preservatives, lubricants, flow-enhancers, filling aids, antioxidants, essences, and other aesthetically pleasing components.

Process for Solubilizing Difficultly Soluble Pharmaceutical Actives

The highly concentrated liquid pharmaceutical compositions are prepared using art-recognized principles and methodologies in mixing the ingredients together and in choosing the type of mixing equipment to be used. In a preferred manner of execution, the difficultly soluble pharmaceutical active, polyethylene glycol, polyvinylpyrrolidone, and solvent are combined and mixed until dissolved to form a homogeneous solution. Any optional components can either be added initially or after the essential components are combined.

Next, the solvent is removed from the resulting homogeneous solution until the residual amount of solvent is present at no more

than from about 0.1 percent to about 6 percent by weight of the composition. The solvents can be removed using any art-recognized evaporation techniques including, but not limited to, rotary evaporation, spray-drying, flash evaporation, film evaporation, 5 freeze-drying, thin film evaporation, forced circulation evaporation, wiped film evaporation, falling film evaporation, and the like. The resulting solution of the difficultly soluble pharmaceutical active, and any optional components, is substantially free from the added alcoholic solvent, i.e., contains no more than 10 from about 0.1 percent to about 6 percent by weight of solvent. This resulting solution is suitable for encapsulation in a soft gelatin capsule using standard encapsulation techniques.

#### Soft Gelatin Capsules

15 Preselected amounts of the highly concentrated liquid pharmaceutical compositions of the present invention can also be encapsulated in a soft gelatin shell. Optionally, the soft gelatin shell is essentially transparent so as to enhance the aesthetic qualities of the capsule. The soft gelatin shells comprise the following essential, as well as optional, components.

#### Gelatin

20 Gelatin is an essential component of the soft gelatin shells of the instant invention. The starting gelatin material used in the manufacture of soft capsules is obtained by the partial hydrolysis of collagenous material, such as the skin, white connective tissues, 25 or bones of animals. Gelatin material can be classified as Type A gelatin, which is obtained from the acid-processing of porcine skins and exhibits an isoelectric point between pH 7 and pH 9; and Type B gelatin, which is obtained from the alkaline-processing of bone and animal (bovine) skins and exhibits an isoelectric point between pH 4.7 and pH 5.2. Blends of Type A and Type B gelatins can be used to obtain a gelatin with the requisite viscosity and bloom strength 30 characteristics for capsule manufacture. Gelatin suitable for capsule manufacture is commercially available from the Sigma Chemical Company, St. Louis, Mo. For a general description of gelatin and gelatin-based capsules, see Remington's Pharmaceutical Sciences, 16th ed., Mack Publishing Company, Easton, Pa. (1980), 35 page 1245 and pages 1576-1582; and U.S. Patent 4,935,243, to Borkan

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et al., issued June 19, 1990; these two references being incorporated herein by reference in their entirety.

5 The soft gelatin shell of the capsules of the instant invention, as initially prepared, comprises from about 20% to about 60% gelatin, more preferably from about 25% to about 50% gelatin, and most preferably from about 40% to about 50% gelatin. The gelatin can be of Type A, Type B, or a mixture thereof with bloom numbers ranging from about 60 to about 300.

Plasticizer

10 A plasticizer is another essential component of the soft gelatin shells of the instant invention. One or more plasticizers is incorporated to produce a soft gelatin shell. The soft gelatin thus obtained has the required flexibility characteristics for use as an encapsulation agent. Useful plasticizers of the present 15 invention include glycerin, sorbitan, sorbitol, or similar low molecular weight polyols, and mixtures thereof.

20 The shell of the present invention, as initially prepared, comprises from about 10% to about 35% plasticizer, preferably from about 10% to about 25% plasticizer, and most preferably from about 10% to about 20% plasticizer. A preferred plasticizer useful in the present invention is glycerin.

Water

25 The soft gelatin shells of the instant invention also comprise water as an essential component. Without being limited by theory, the water is believed to aid in the rapid dissolution or rupture of the soft gelatin shell upon contact with the gastrointestinal fluids encountered in the body.

30 The shell of the present invention, as initially prepared, comprises from about 15% to about 50% water, more preferably from about 25% to about 40% water, and most preferably from about 30% to about 40% water.

Optional Components

35 Other optional components which can be incorporated into the soft gelatin shells include colorings, flavorings, preservatives, anti-oxidants, essences, and other aesthetically pleasing components.

Soft Gelatin Shell Preparation and Encapsulation

The solubilized pharmaceutical compositions of the present invention can be encapsulated within any conventional soft gelatin shell that is capable of substantially containing the composition for a reasonable period of time. The soft gelatin shells of the instant invention can be prepared by combining appropriate amounts of gelatin, water, plasticizer, and any optional components in a suitable vessel and agitating and/or stirring while heating to about 65°C until a uniform solution is obtained. This soft gelatin shell preparation can then be used for encapsulating the desired quantity of the solubilized fill composition employing standard encapsulation methodology to produce one-piece, hermetically-sealed, soft gelatin capsules. The gelatin capsules are formed into the desired shape and size so that they can be readily swallowed. The soft gelatin capsules of the instant invention are of a suitable size for easy swallowing and typically contain from about 100 mg to about 2000 mg of the solubilized pharmaceutical active composition. Soft gelatin capsules and encapsulation methods are described in P.K. Wilkinson et al., "Softgels: Manufacturing Considerations", Drugs and the Pharmaceutical Sciences, 41 (Specialized Drug Delivery Systems), P. Tyle, Ed. (Marcel Dekker, Inc., New York, 1990) pp.409-449; F.S. Hom et al., "Capsules, Soft", Encyclopedia of Pharmaceutical Technology, vol. 2, J. Swarbrick and J.C. Boylan, eds. (Marcel Dekker, Inc., New York, 1990) pp. 269-284; M.S. Patel et al., "Advances in Softgel Formulation Technology", Manufacturing Chemist, vol. 60, no. 7, pp. 26-28 (July 1989); M.S. Patel et al., "Softgel Technology", Manufacturing Chemist, vol. 60, no. 8, pp. 47-49 (August 1989); R.F. Jimerson, "Softgel (Soft Gelatin Capsule) Update", Drug Development and Industrial Pharmacy (Interphex '86 Conference), vol. 12, no. 8 & 9, pp. 1133-1144 (1986); and W.R. Ebert, "Soft Elastic Gelatin Capsules: A Unique Dosage Form", Pharmaceutical Technology, vol. 1, no. 5, pp. 44-50 (1977); these references are incorporated by reference herein in their entirety. The resulting soft gelatin capsule is soluble in water and in gastrointestinal fluids. Upon swallowing the capsule, the gelatin shell rapidly dissolves or ruptures in the gastrointestinal tract thereby introducing the pharmaceutical actives into the physiological system.

EXAMPLES

5 The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

Ingredients are identified by chemical or CTFA name.

EXAMPLE I10 Solubilized Acetaminophen Composition

A highly concentrated solution containing acetaminophen is prepared from the following ingredients.

	<u>Ingredient</u>	<u>Weight %</u>
15	Acetaminophen	26.00
	Polyethylene Glycol 600	52.00
	Polyvinylpyrrolidone <sup>1</sup>	3.00
	Ethanol 95% USP	QS100

1 Available as Plasdone<sup>R</sup> K-29/32 from GAF Chemicals Co.

20 The acetaminophen, polyethylene glycol 600, polyvinylpyrrolidone, and ethanol are combined in a suitable vessel and mixed at room temperature until a homogeneous solution is obtained. Next, the ethanol is removed by rotary evaporation at room temperature. The resulting acetaminophen composition is substantially free from ethanol and water, is suitable for oral administration, and contains about 32.10% acetaminophen, 64.20% polyethylene glycol 600, and about 3.70% polyvinylpyrrolidone.

EXAMPLE II25 Soft Gelatin Capsule Containing A Solubilized Acetaminophen Composition

30 A soft gelatin mixture is first prepared from the following ingredients.

	<u>Ingredient</u>	<u>Weight %</u>
35	Gelatin	47.00
	Glycerin	15.00
	Water	QS100

The above ingredients are combined in a suitable vessel and heated with mixing at about 65°C to form a uniform solution. Using

standard encapsulation methodology, the resulting solution is used to prepare soft gelatin capsules containing approximately 1000 mg of the acetaminophen composition of Example I. The resulting soft gelatin acetaminophen capsules are suitable for oral administration.

5

EXAMPLE IIISolubilized Pharmaceutical Composition

A highly concentrated solution containing acetaminophen in combination with other pharmaceutical actives is prepared from the following ingredients.

	<u>Ingredient</u>	<u>Weight %</u>
10	Acetaminophen	25.00
	Pseudoephedrine Hydrochloride	3.00
	Dextromethorphan Hydrobromide	1.49
	Doxylamine Succinate	0.38
15	Polyethylene Glycol 600	46.20
	Polyvinylpyrrolidone <sup>1</sup>	2.50
	Ethanol 95% USP	QS100

<sup>1</sup> Available as Plasdone<sup>R</sup> K-29/32 from GAF Chemicals Co.

The acetaminophen, pseudoephedrine hydrochloride, dextromethorphan hydrobromide, doxylamine succinate, polyethylene glycol 600, polyvinylpyrrolidone, and ethanol are combined in a suitable vessel and mixed at room temperature until a uniform solution is formed. Next, the ethanol is removed by rotary evaporation at room temperature. The resulting pharmaceutical composition is substantially free from ethanol and water, is suitable for oral administration, and contains about 31.82% acetaminophen, 3.82% pseudoephedrine hydrochloride, 1.90% dextromethorphan hydrobromide, 0.48% doxylamine succinate, 58.80% polyethylene glycol 600, and 3.18% polyvinylpyrrolidone.

30

EXAMPLE IVSoft Gelatin Capsule Containing A Solubilized Acetaminophen Composition

A gelatin solution is prepared as described in Example II. Using standard encapsulation methodology, this gelatin solution is used to prepare soft gelatin capsules containing approximately 1000 mg of the pharmaceutical composition of Example III. The resulting

soft gelatin pharmaceutical capsules are suitable for oral administration.

EXAMPLE V

Solubilized Pharmaceutical Composition

5 A highly concentrated solution containing acetaminophen in combination with other pharmaceutical actives is prepared from the following ingredients.

	<u>Ingredient</u>	<u>Weight %</u>
10	Acetaminophen	23.20
	Pseudoephedrine Hydrochloride	2.78
	Dextromethorphan Hydrobromide	1.39
	Doxylamine Succinate	0.58
	Polyethylene Glycol 600	46.47
15	Polyvinylpyrrolidone <sup>1</sup>	1.86
	Propylene Glycol	3.72
	Ethanol 95% USP	QS100

1 Available as Plasdone<sup>R</sup> K-29/32 from GAF Chemicals Co.

20 The acetaminophen, pseudoephedrine hydrochloride, dextromethorphan hydrobromide, doxylamine succinate, polyethylene glycol 600, polyvinylpyrrolidone, propylene glycol, and ethanol are combined in a suitable vessel and mixed at room temperature until a homogeneous solution is formed. Next, the ethanol is removed by rotary evaporation. The resulting pharmaceutical composition is substantially free from ethanol and water, is suitable for oral administration, and contains about 29.00% acetaminophen, 3.48% pseudoephedrine hydrochloride, 1.74% dextromethorphan hydrobromide, 0.72% doxylamine succinate, 58.09% polyethylene glycol 600, 2.32% polyvinyl- pyrrolidone, and 4.64% propylene glycol.

EXAMPLE VI

30 Soft Gelatin Capsule Containing a Solubilized Pharmaceutical Composition

35 A gelatin solution is prepared as described in Example II. Using standard encapsulation methodology, this gelatin solution is used to prepare soft gelatin capsules containing approximately 1000 mg of the pharmaceutical composition of Example V. The resulting soft gelatin pharmaceutical capsules are suitable for oral administration.

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EXAMPLE VIISolubilized Pharmaceutical Composition

A highly concentrated solution containing acetaminophen in combination with other pharmaceutical actives is prepared from the following ingredients.

	<u>Ingredient</u>	<u>Weight %</u>
	Acetaminophen	22.22
	Pseudoephedrine Hydrochloride	2.67
	Dextromethorphan Hydrobromide	0.89
10	Guaifenesin	8.89
	Polyethylene Glycol 600	40.00
	Polyvinylpyrrolidone <sup>1</sup>	1.78
	Propylene Glycol	3.56
	Ethanol 95% USP	QS100

15       1 Available as Plasdone<sup>R</sup> K-29/32 from GAF Chemicals Co.

The acetaminophen, pseudoephedrine hydrochloride, dextromethorphan hydrobromide, guaifenesin, polyethylene glycol 600, polyvinylpyrrolidone, propylene glycol, and ethanol are combined in a suitable vessel and mixed at room temperature until a homogeneous solution is formed. Next, the ethanol is removed by rotary evaporation. The resulting pharmaceutical composition is substantially free from ethanol and water, is suitable for oral administration, and contains about 27.77% acetaminophen, 3.34% pseudoephedrine hydrochloride, 1.11% dextromethorphan hydrobromide, 11.11% guaifenesin, 49.99% polyethylene glycol 600, 2.22% polyvinylpyrrolidone, and 4.45% propylene glycol.

EXAMPLE VIIISoft Gelatin Capsule Containing a Solubilized Pharmaceutical Composition

30       A gelatin solution is prepared as described in Example II. Using standard encapsulation methodology, this gelatin solution is used to prepare soft gelatin capsules containing approximately 1000 mg of the pharmaceutical composition of Example VII. The resulting soft gelatin pharmaceutical capsules are suitable for oral administration.

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EXAMPLE IXSolubilized Pharmaceutical Composition

A highly concentrated solution containing acetaminophen in combination with other pharmaceutical actives is prepared from the following ingredients.

	<u>Ingredient</u>	<u>Weight %</u>
	Acetaminophen	25.26
	Pseudoephedrine Hydrochloride	3.03
	Dextromethorphan Hydrobromide	1.52
5	Chlorpheniramine Maleate	0.20
10	Polyethylene Glycol 600	43.91
	Polyvinylpyrrolidone <sup>1</sup>	2.02
	Propylene Glycol	4.04
	Ethanol 95% USP	QS100

15       <sup>1</sup> Available as Plasdone<sup>R</sup> K-29/32 from GAF Chemicals Co.

The acetaminophen, pseudoephedrine hydrochloride, dextromethorphan hydrobromide, chlorpheniramine maleate, polyethylene glycol 600, polyvinylpyrrolidone, propylene glycol, and ethanol are combined in a suitable vessel and mixed at room temperature until a homogeneous solution is formed. Next, the ethanol is removed by rotary evaporation. The resulting pharmaceutical composition is substantially free from ethanol and water, is suitable for oral administration, and contains about 31.58% acetaminophen, 3.79% pseudoephedrine hydrochloride, 1.90% dextromethorphan hydrobromide, 0.25% chlorpheniramine maleate, 54.90% polyethylene glycol 600, 2.53% polyvinylpyrrolidone, and 5.05% propylene glycol.

EXAMPLE XSoft Gelatin Capsule Containing a Solubilized Pharmaceutical Composition

30       A gelatin solution is prepared as described in Example II. Using standard encapsulation methodology, this gelatin solution is used to prepare soft gelatin capsules containing approximately 1000 mg of the pharmaceutical composition of Example IX. The resulting soft gelatin pharmaceutical capsules are suitable for oral administration.

35       WHAT IS CLAIMED IS:

1. A process for solubilizing difficultly soluble pharmaceutical actives, comprising the steps of:
  - (a) combining and mixing until dissolved
    - (i) from about 1% to about 40% of at least one difficultly soluble pharmaceutical active, preferably from about 15% to about 35%, most preferably from about 20% to about 30%.
    - (ii) from about 20% to about 70% of a polyethylene glycol,
    - (iii) from about 1% to about 28% of a polyvinylpyrrolidone, and
    - (iv) from about 1% to about 50% of a solvent selected from the group consisting of the monohydric alcohols having from 1 to 4 carbon atoms and mixtures thereof, preferably wherein said solvent is ethanol, wherein the ratio of said polyethylene glycol to said polyvinylpyrrolidone is at least about 2.5:1; and
  - (b) evaporating said solvent to obtain a composition containing from about 0.1% to about 6% by weight of said solvent.
  2. A process according to Claim 1 wherein said polyethylene glycol is added in an amount from about 30% to about 60% and said polyvinylpyrrolidone is added in an amount from about 1% to about 10% and preferably wherein said polyethylene glycol is added in an amount from about 40% to about 50% and said polyvinylpyrrolidone is added in an amount from about 1% to about 5%.
  3. A process according to Claim 2 wherein said difficultly soluble pharmaceutical active is selected from the group consisting of acetaminophen, acetylsalicylic acid, ibuprofen, fenuprofen, fenoprofen, flurbiprofen, indomethacin, naproxen, and mixtures thereof, and preferably wherein said active is acetaminophen.

4. A process according to Claim 3 wherein said polyethylene glycol is selected from the group consisting of PEG-6, PEG-8, PEG-9, PEG-10, PEG-12, PEG-14, PEG-16, PEG-18, PEG-20, and mixtures thereof, preferably wherein said polyethylene glycol is PEG-12; and wherein said polyvinylpyrrolidone has an average molecular weight of about 9,000 to about 45,000, preferably about 29,000.
5. A process according to Claim 1 which further comprises combining in step (a) from about 0.5% to about 20% of a second pharmaceutical active selected from the group consisting of dextromethorphan hydrobromide, doxylamine succinate, pseudoephedrine hydrochloride, chlorpheniramine maleate, guaifenesin, triprolidine hydrochloride, diphenhydramine hydrochloride, and mixtures thereof.
6. A process for preparing soft gelatin capsules of a highly-concentrated liquid, pharmaceutical composition, comprising the steps of:
  - (a) combining and mixing until dissolved
    - (i) from about 1% to about 40% of at least one difficultly soluble pharmaceutical active,
    - (ii) from about 20% to about 70% of a polyethylene glycol,
    - (iii) from about 1% to about 28% of a polyvinylpyrrolidone, and
    - (iv) from about 1% to about 50% of a solvent selected from the group consisting of monohydric alcohols having from one to four carbon atoms and mixtures thereof, preferably wherein said solvent is ethanol, wherein the ratio of said polyethylene glycol to said polyvinylpyrrolidone is at least about 2.5:1;
  - (b) evaporating said solvent to obtain a composition containing from about 0.1% to about 6% by weight of said solvent; and
  - (e) encapsulating the evaporated composition in a soft gelatin shell.

7. A process according to Claim 6 wherein said difficultly soluble pharmaceutical active is selected from the group consisting of acetaminophen, acetylsalicylic acid, ibuprofen, fenuprofen, fenoprofen, flurbiprofen, indomethacin, naproxen, and mixtures thereof, and preferably wherein said active is acetaminophen.
8. A process according to Claim 7 which further comprises combining in step (a) from about 0.5% to about 20% of a second pharmaceutical active selected from the group consisting of dextromethorphan hydrobromide, doxylamine succinate, pseudoephedrine hydrochloride, chlorpheniramine maleate, guaifenesin, triprolidine hydrochloride, diphenhydramine hydrochloride, and mixtures thereof.
9. A highly-concentrated liquid, pharmaceutical composition prepared in accordance with the process of any of Claims 1-5.
10. A soft gelatin capsule prepared in accordance with the process of any of Claims 6-8.
11. A highly-concentrated liquid, pharmaceutical composition which is substantially free from solvent, comprising:
  - (a) from about 1.25% to about 50% of at least one difficultly soluble pharmaceutical active;
  - (b) from about 25% to about 87.5% of a polyethylene glycol;
  - (c) from about 1.25% to about 35% of a polyvinyl-pyrrolidone; and
  - (d) from about 0.1% to about 8% water;wherein the ratio of said polyethylene glycol to said polyvinylpyrrolidone is at least about 2.5:1.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 92/04771

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)<sup>6</sup>

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.C1. 5 A61K9/48; A61K47/10

## II. FIELDS SEARCHED

Minimum Documentation Searched<sup>7</sup>

Classification System	Classification Symbols
Int.C1. 5	A61K

Documentation Searched other than Minimum Documentation  
to the Extent that such Documents are Included in the Fields Searched<sup>8</sup>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup>

Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
Y	WO,A,8 802 625 (R.P. SCHERER CORPORATION) 21 April 1988 cited in the application see page 10, line 1 - line 19 see page 14, line 27 - page 15, line 6 see page 16; table 4 see page 19; example 1 see page 20; example 3 see claims 1,2,7,8 ---	1-11
Y	EP,A,0 042 076 (A. NATTERMANN & CIE GMBH) 23 December 1981 see page 4, line 23 - page 5, line 29 see page 6, line 13 - line 32 see page 7, line 16 - page 9, line 17 see page 11; examples 5,7 see claims ---	1-4,6-7, 9-11 ---

\* Special categories of cited documents :<sup>10</sup>

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reasons (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z" document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search

08 OCTOBER 1992

Date of Mailing of this International Search Report

09. 11. 92

International Searching Authority

EURPEAN PATENT OFFICE

Signature of Authorized Officer

BOULOIS D.



III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		Relevant to Claim No.
Category	Citation of Document, with indication, where appropriate, of the relevant passages	
Y	US,A,4 777 050 (W.A. VADINO) 11 October 1988 see column 3 - column 4; example 1	5,8
A	EP,A,0 152 292 (R.P. SCHERER CORPORATION) 21 August 1985 see page 16 - page 17; example 1	3
A	DE,A,2 546 371 (SANDOZ PATENT GMBH) 21 April 1977 see page 6 - page 7; example 1	1
	see claims	
A	GB,A,2 184 654 (BAYER A.G.) 1 July 1987 see page 1, line 33 - line 56 see page 3; example 7	1-11
A	EP,A,0 193 287 (NIPPON KAYAKU KABUSHIKI KAISHA) 3 September 1986 see page 10; example 4 see claims 1,4,5,7	1-11
A	FR,A,2 237 619 (R.P. SCHERER LIMITED) 14 February 1975 see page 1, line 26 - page 2, line 3 see page 3; example 1	1-11